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Both solubility and chemical stability of curcumin are enhanced by solid dispersion in cellulose derivative matrices

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ABSTRACT

Amorphous solid dispersions (ASD) of curcumin (Cur) in cellulose derivative matrices, hydroxypropylmethylcellulose acetate succinate (HPMCAS), carboxymethylcellulose acetate butyrate (CMCAB), and cellulose acetate adipate propionate (CAAdP) were prepared in order to investigate the structure–property relationship and identify polymer properties necessary to effectively increase Cur aqueous solution concentration. XRD results indicated that all investigated solid dispersions were amorphous, even at a 9:1 Cur:polymer ratio. Both stability against crystallization and Cur solution concentration from these ASDs were significantly higher than those from physical mixtures and crystalline Cur. Remarkably, curcumin was also stabilized against chemical degradation in solution. Chemical stabilization was polymer-dependent, with stabilization in CAAdP > CMCAB > HPMCAS > PVP, while matrices enhanced solution concentration as PVP > HPMCAS ≫ CMCAB ≈ CAAdP. HPMCAS/Cur dispersions have useful combinations of pH-triggered release profile, chemical stabilization, and strong enhancement of Cur solution concentration.

1. Introduction

Curcumin (Fig. 1) is a hydrophobic polyphenol derived from the rhizome of turmeric (*Curcuma longa*), widely used as a natural yellow pigment in the food and textile industries. Recently curcumin has received increasing attention for its beneficial properties including anti-oxidant, anti-cancer, and anti-inflammatory effects (Aggarwal & Harikumar, 2009). Phase I clinical trials confirmed the safety of curcumin doses up to 12 g daily, with no significant toxicity (Lao et al., 2006; Shoba, 1998). However, the poor oral bioavailability of curcumin has been thoroughly demonstrated in both animals and humans (Anand, Kunnumakkara, Newman & Aggarwal, 2007), and is due to factors including poor aqueous solubility, chemical instability, and metabolic susceptibility. Maximum Cur solubility in aqueous buffer (pH 5.0) is reportedly only 11 ng/mL (Tonnesen, Masson & Loftsson, 2002); at neutral pH Cur concentration is too low to quantify. Curcumin also degrades quickly in neutral or alkaline buffer solution (Priyadarsini, 2009; Wang et al., 1997). Therefore, drug delivery systems that would increase solubility and chemical stability of Cur are important targets for those seeking to enable its use for enhancing human health. Since the "call to arms" to develop enhanced flavonoid delivery methods flavonoids in 2007 (Hu, 2007), many researchers have sought to enhance Cur water solubility, stability and bioavailability (Anand et al., 2007). Although alternatives for Cur administration have been explored (e.g., intravenous, transdermal) (Patel & Patel, 2009), oral bioavailability is still very important since oral administration is the most convenient and practical way to administer drugs, particularly for daily or more frequent administration. In order to enhance oral bioavailability, researchers have recently investigated strategies including chemical modification (Tang et al., 2010; Wan et al., 2010), and novel formulations including nanoparticles (Mohanty & Sahoo, 2010; Yen, Wu, Tzeng, Lin & Lin, 2010), micelles (Mohanty, Acharya, Mohanty, Dilnawaz & Sahoo, 2010; Yu & Huang, 2010), cyclodextrin complexes (Singh, Tonnesen, Vogensen, Loftsson & Masson, 2010; Yadav et al., 2010; Yallapu, Jaggi & Chauhan, 2010), microemulsions (Wu, Xu, Huang & Wen, 2011) and solid dispersions (Onoue et al., 2010b; Phaechamud & Sotanaphun, 2010). Use of piperine as metabolic inhibitor is another interesting approach, which may improve Cur bioavailability up to 20-fold by inhibition of glucuronidation (Shoba, 1998). Recently Wu et al. formulated Cur in a self-microemulsifying drug delivery system (SMEDDS), affording [Cur] 50 mg/mL, and 1213% relative oral bioavailability vs. Cur suspension (Wu et al., 2011).

Curcumin would appear to be an excellent candidate for solubility enhancement by ASD, since it is only moderately hydrophobic (log *P* 2.5), but with a high MP (180 °C). ASD is a promising way to

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Fig. 1. Chemical structures of Cur in keto-enol tautomeric equilibrium.

improve oral drug solubility and bioavailability, especially recently as issues of formulation stability have been successfully addressed (Leuner & Dressman, 2000; Qian, Huang & Hussain, 2010; Singh, Sayyad & Sawant, 2010; Timpe, 2010; Tiwari, 2009). Crystalline drugs often exhibit poor water solubility, since the lattice energy must be overcome in order for dissolution to occur. Molecular dispersion of the drug in a polymer matrix traps it in an ASD; dissolution from this ASD may afford a supersaturated drug solution. These molecular drug–polymer dispersions may be prepared by co-extrusion, or dissolution of drug and polymer in a common solvent followed by co-precipitation into a common non-solvent, spray-drying, freeze-drying, rotary evaporation, or film casting. Polymers known to be safe for pharmaceutical use have received the most attention in ASDs, including PVP and polysaccharide derivatives like hydroxypropylmethylcellulose (HPMC) and HPMCAS (Leuner & Dressman, 2000). We postulate three key polymer performance characteristics for ASDs, listed with some key polymer properties that may provide them; (1) stabilize drug against crystallization in the solid phase (miscibility, specific polymer–drug interactions, high glass transition temperature (T_g)); (2) stabilize drug in solution after release but before absorption from the GI tract (at least slight (μg/mL) polymer solubility in pH 6.8 buffer, plus affinity for drug as in (1)); (3) desired drug release profile (release rate declines as polymer hydrophobicity rises, groups ionizable at neutral pH (e.g., $-CO_2H$) can provide a release trigger). Properly designed carboxylated polysaccharides are excellent candidate ASD polymers since as a class they have low toxicity and high T_g values; high T_g can maintain the matrix in the glassy state even at high humidity and relatively high ambient temperatures, limiting drug molecular motion and thus inhibiting crystallization in storage and transport. Recently, HPMCAS and CMCAB ASDs have been shown to improve water solubility and bioavailability of poorly water-soluble drugs (Friesen et al., 2008; Shelton et al., 2009).

Several authors have reported solubility enhancement of Cur by ASD (Kaewnopparat et al., 2009; Onoue et al., 2010b; Paradkar, Ambike, Jadhav & Mahadik, 2004; Phaechamud & Sotanaphun, 2010). Suresh et al. reported using Cremophor and PEG 20000 to achieve 18 mg/mL [Cur] (Suresh & Prasad, 1999). Onoue and co-workers reported preparation of Cur nanocrystals, HPMCAS solid dispersions, and nanoemulsions. They observed enhanced (up to 9–16X) Cur solubility and oral bioavailability, including 12X enhancement by solid dispersion at 1:4 curcumin:HPMCAS (impacts of choice of cellulose derivative or flavonoid:polymer ratio were not reported) (Onoue et al., 2010b). Paradkar and Kaewnopparat found (Kaewnopparat et al., 2009; Paradkar et al., 2004) that Cur:PVP may form spray-dried ASDs in ratios ranging from 1:8 to 1:2, and that both Cur solubility and dissolution rate were much greater than those from physical Cur:PVP mixtures or pure curcumin.

Herein we report studies of Cur solubility enhancement using spray dried ASDs with three cellulose derivatives (HPMCAS and CMCAB, as well as CAAdP, a new cellulose ester specifically designed for ASD (Kar, Liu & Edgar, 2011)). We investigated the impact of polymer structure upon stabilization of amorphous curcumin in the solid phase, dissolution, and stabilization of curcumin against crystallization from the supersaturated solution phase generated upon ASD dissolution. We evaluated the effect of Cur/polymer ratio and compared with pure curcumin and Cur/PVP ASDs. We also report the unexpected ability of these cellulose derivatives to stabilize curcumin against chemical decomposition in solution.

2. Experimental

2.1. Chemicals

Curcumin (98+ %), poly(vinylpyrrolidinone) (PVP, K29-32, M_W 58,000) and potassium bromide (99+ %, for spectroscopy, IR grade) were supplied by Acros Organics (Geel, Belgium). Carboxymethylcellulose acetate butyrate (CMCAB-641-0.2) was from Eastman Chemical; degree of substitution (DS) (carboxymethyl) = 0.33, DS (butyryl) = 1.64, DS (acetyl) = 0.44, M_w = 20,000. Hydroxypropylmethylcellulose acetate succinate (HPMCAS) (AS-LG) was from Shin-Etsu Chemical Co., Ltd; DS(acetyl) = 0.47, DS(succinoyl) = 0.40, DS(methyl) 1.87, molar substitution (MS) (hydroxypropyl) = 0.25, M_w 18,000. Cellulose acetate adipate propionate (CAAdP) was synthesized as previously described (Kar et al., 2011); DS(adipoyl) = 0.33, DS(acetyl) = 0.04, DS(propionyl) = 2.09, M_w 12,000. Acetone (high-pressure liquid chromatography (HPLC) grade, 0.2 micron filtered), reagent alcohol (ethanol), potassium phosphate monobasic, and sodium hydroxide were supplied by Fisher Scientific. Buffer solutions were prepared according to USP30-NF25.

2.2. Preparation of spray-dried solid dispersions

Cur/matrix (10.0 g; wt ratios 1:9, 1:3, 1:1, 3:1 and 9:1) was dissolved in acetone/ethanol (1/4) to make a 20 g/L solution. ASDs were prepared using a Buchi mini-spray dryer B-290 equipped with nitrogen purge for use with organic solvents. Operating parameters: inlet temperature, 90 °C; outlet temperature, 57–60 °C; feed rate, 9 mL/min; nitrogen flow 350 L/h. Weight yield of the spray-drying process was approximately 50–60%.

Physical Cur/polymer mixtures were made by grinding with a mortar and pestle.

2.3. Characterization of the spray-dried curcumin/matrix solid dispersions

ASDs were characterized by comparing infrared (IR) spectra, nuclear magnetic resonance (NMR) spectra, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) patterns vs. pure components and physical blends.

2.4. IR spectroscopy

Solutions were prepared by dissolving drug and polymer at different ratios in acetone/ethanol 1:4 (by weight). All mixtures were visually inspected to confirm that solids were fully dissolved, forming uniform one-phase solutions. Solutions (2–3 drops) were placed on ZnS Cleartran substrates, which were immediately rotated on a KW-4A spin coater at 500/2500 rpm for 18 and 30 s respectively. Since curcumin is a slow crystallizer, amorphous films of curcumin and of polymer/curcumin dispersions could be readily prepared in this way; analysis of the amorphous dispersions in the proper polymer/Cur ratio is preferred to analysis of the corresponding spray-dried powder samples, since it permits acquisition of IR spectra in the transmission mode, avoiding artifacts generated by mixing particles with KBr, or when using ATR (e.g. moisture sorption by sample, and wavelength dependent penetration of the light) and is the most rigorous method when evaluating hydrogen bonding interactions (Van Eerdenbrugh & Taylor, 2010). Infrared spectra of the resulting thin films were obtained in absorbance mode using a Bio-Rad FTS 6000 spectrophotometer (Bio-Rad Laboratories, Hercules, CA) equipped with globar infrared source, KBr

beamsplitter, and DTGS detector. Scan range was set from 500 to 4000 cm^{-1} with 4 cm^{-1} resolution, and 128 scans were co-added. Absorbance intensity of the spectral region of interest was 0.6–1.0. During measurements, spin-coated samples and the spectrophotometer sample compartment were flushed with dry air.

2.5. NMR spectroscopy

^1H NMR spectra in acetone-d_6 were recorded on an Inova 400M instrument with TMS internal reference (at 400 MHz, δ in ppm, room temperature, 64 scans, curcumin concentration 10 mg/mL).

2.6. XRD analysis

XRD measurements used a Bruker D8 Discovery X-Ray Diffractometer, at a voltage of 40 kV and 25 mA. The scanned angle was set as $5 < 2\theta < 40^\circ$ and scan rate was 2°/min.

2.7. DSC measurement

Heating curves of curcumin and solid dispersion were obtained using modulated DSC (Model Q2000, TA Instruments, New Castle, Delaware) equipped with refrigerated cooling accessory. A 2–5 mg sample was packed in a non-hermetically crimped aluminum pan, and heated under dry nitrogen. Samples were heated from 25 °C to 100–120 °C at 10 °C/min then quickly cooled to 25 °C at 100 °C/min to eliminate moisture and relieve stress, then heated from 25 °C to 200 °C at 10 °C/min; transitions are reported from this second heating scan. DSC heating curves were analyzed using Universal Analysis 2000 software (TA Instruments).

2.8. Film preparation

Polymer, Cur, and ASD solutions in acetone or ethanol (10 mg/mL) were spin-coated onto silicon wafers at room temperature using a WS-400-6NPP/LITE spin coater (Laurell Technologies Corporation). Spinning velocity was 4000 rpm and spinning time was 60 s.

2.9. Contact angle measurements

Contact angles were measured on spin-coated films prepared as described above. The apparatus (FTA 200 dynamic contact angle analyzer, First Ten Angstroms, USA) was equipped with a magnifying video camera that automatically captured water droplet images during 8.5 s following measurement initiation.

2.10. UV–vis spectroscopy

UV–vis spectra were recorded on a Thermo Scientific Evolution 300 UV–Visible Spectrometer.

2.11. Measurement of solubility of the matrix polymers

Polymer (0.5 g; CMCAB, HPMCAS or PVP) was dispersed in 10 mL pH 6.8 buffer solution. The suspension was mixed (vortex mixer) for 1 min, then ultrasonicated (15 min), then shaken (24 h, room temperature, Burrell wrist action shaker (Model 75)). The suspension/solution was centrifuged (14,000 × *g*, 10 min) to remove insoluble material. An aliquot (1 mL) of the top, clear solution was withdrawn and solvent was evaporated in an oven (80 °C, 5 h). Dissolved polymer weight was calculated by subtracting the weight of salt in buffer solution (7.7 mg/mL calculated from weight of KH_2PO_3 and NaOH in 1 L pH 6.8 buffer) from the residue weight. Dissolved polymer concentration (w/v) was then calculated by dividing dissolved polymer weight by volume of solution withdrawn.

2.12. Curcumin calibration curves

Creation of a calibration curve for poorly soluble species like Cur is challenging, since it is difficult to reach required concentrations in the most pertinent medium, aqueous buffer, in the absence of stabilizing polymer. Stability of the Cur excited state and position of the keto-enol equilibrium may be impacted by the solvent (Shen & Ji, 2007). From Cur standard curves (Fig S1), the Cur extinction coefficient changes significantly from 142 $L\,g^{-1}\,cm^{-1}$ (ethanol) to 66 $L\,g^{-1}\,cm^{-1}$ (pH 6.8 buffer). Such a large difference cannot be explained only by solvent polarity differences, since both ethanol and water are polar solvents. The most likely reason is fast Cur crystallization and/or degradation upon dilution of ethanolic curcumin solution with aqueous buffer. The similar coefficients of curcumin in pH 6.8 and 1.2 buffer indicate that crystallization may dominate, since Cur stability at pH 1.2 is much higher than that at pH 6.8 (vide infra). Interestingly, the extinction coefficient in pH 6.8 buffer increased to 99 and 106 $L\,g^{-1}\,cm^{-1}$ in the presence of 0.63 g/L of HPMCAS and PVP, respectively, presumably due primarily to polymer inhibition of Cur crystallization. Neither PVP nor HPMCAS absorb at 427 nm. We consequently used UV/Vis calibration curves of Cur in ethanol to avoid issues arising from crystallization and nanoparticle formation.

A curcumin standard curve in ethanol was generated for the calculation of [Cur] by UV–vis. The effect of adding small amounts (up to 5 v%) of water or aqueous buffer (pH 6.8) to ethanol was studied. Calibration curves in aqueous buffer (pH 6.8 or 1.2) were generated by dilution of Cur solution in ethanol (1.0 mg/mL, 10–200 μl) with buffer solution to 10 mL. To study the effect of polymer matrix on the standard curve, the Cur ethanol stock solution (1 mg/mL) was also diluted by the solution of PVP or HPMCAS (0.63 mg/mL) in pH 6.8 buffer or PVP (0.63 mg/mL) in pH 1.2 buffer. Due to low solubility of CMCAB in pH 6.8 and 1.2 buffers and HPMCAS in pH 1.2 buffer, Cur standard curves in the presence of CMCAB and HPMCAS in pH 1.2 buffer were not measured.

2.13. Dissolution testing

Curcumin ASD (Cur content fixed at 50 mg) was dispersed in 10 mL of pH 6.8 phosphate buffer in an amber flask with shaking at room temperature by a Burrell wrist action shaker (Model 75) to equilibrium (determined by measured solution [Cur]). The suspension was centrifuged (14,000 × *g*, 10 min) to remove insoluble material. To study the effect of centrifugation conditions, comparative experiments (70,000 × *g*, 30 min) for Cur/PVP and Cur/HPMCAS ASDs were run. Supernatant [Cur] was determined by UV–vis using the ethanol calibration curve generated as described above.

2.14. Enhancement of curcumin stability

Solution stability by UV–vis: Curcumin or Cur ASDs (Cur/CMCAB (1/9) or Cur/PVP (1/9)) were dissolved in ethanol with Cur concentration fixed at 1 mg/mL. Cur/HPMCAS (1/9) and Cur/CAAdP (1/9) ASDs were dissolved in THF due to limited solubility in ethanol. The appropriate stock solution (125 μl) was diluted to 10 mL with pH 6.8 or 7.4 buffer solution. UV–vis absorption of diluted solutions (theoretical maximum [Cur] = 12.5 μg/mL) was measured at time intervals from 0.5 to 24 h.

Chemical stability by UV–vis: Aliquots of 25 μL of Cur or Cur/polymer 1/9 ASD dissolved in ethanol or THF as described above ([Cur] = 1 mg/mL) were added to 975 μL of 0.2 M pH 7.4 or 6.8 buffer. Samples were incubated at room temperature for indicated times. After incubation, the reaction mixtures were diluted by

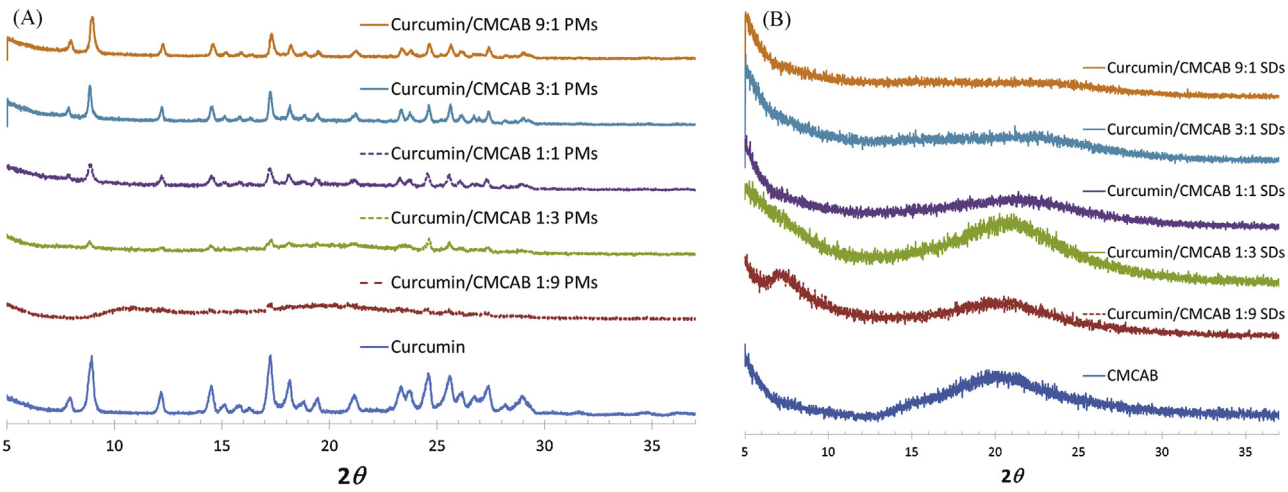

Fig. 2. XRPD patterns of Cur/CMCAB physical mixtures (A) and spray dried solid dispersions (B).

1 mL of ethanol and the UV–vis absorption of the diluted solutions (theoretical maximum [Cur] 12.5 μg/mL) was measured.

Chemical stability by HPLC: Aliquots of 50 μL of Cur or Cur/polymer 1/9 ASD dissolved in ethanol or THF as described above ([Cur] = 1 mg/mL) were added to 955 μL portions of 0.2 M pH 7.4 buffer. Samples were incubated at room temperature for the indicated times. After incubation, the reaction mixtures were diluted by 1 mL of ethanol; then the solution (theoretical [Cur] = 0.025 mg/mL) was filtered through a 1 μm PVDF membrane filter, and the filtrate analyzed by HPLC (Agilent 1200 series HPLC equipped with 1200 quaternary pump, variable wavelength UV/Vis detector and Eclipse XDB-C18 column (150 × 4.6 mm, 5 μm particle size) using 40% THF, 60% water and 1% acetic acid (pH 3.0) as mobile phase) (Wang et al., 1997).

2.15. Curcumin release profile

Cur release was measured as follows. Samples (pure Cur, physical mixture or ASD) were dispersed in 100 mL pH 6.8 buffer solution in an amber glass flask with [Cur] 0.07 mg/mL, with stirring (stir bar) at 25 °C. Aliquots (1.5 mL) were withdrawn at appropriate time intervals and replaced with 1.5 mL of fresh dissolution medium to maintain constant volume. UV–vis absorption of aliquots was recorded before and after centrifugation at 4550, 14,000 or 70,000 × *g* for 10 min. To confirm nanoparticle removal from the aqueous Cur solution, the UV absorption of solutions from Cur/PVP 1/9 and Cur/HPMCAS 1/9 ASDs was remeasured after filtering (0.2 μm pore size membrane filter). Drug release profiles of Cur, Cur/PVP 1/9, Cur/HPMCAS 1/9 and Cur/CMCAB 1/9 ASDs in pH 1.2 buffer were measured using the same method and aliquots were centrifuged before UV–vis measurement.

3. Results and discussion

The polysaccharides were chosen, and in the case of CAAdP, designed, to effectively stabilize amorphous curcumin and release it at small intestine pH. Thus CMCAB, HPMCAS and CAAdP are fundamentally hydrophobic polymers (for miscibility with hydrophobic actives such as curcumin), composed of low toxicity components like cellulose, acetic acid, and adipic or succinic acid, with a pendent carboxyl group providing not only pH-triggered swelling and active release, but also specific interactions with hydrogen-bonding groups on the drug, promoting molecular dispersion. Our working hypothesis is that, in addition to characteristics elucidated above that allow amorphous matrix polymers to stabilize the active molecule in the solid phase, and release said molecule at the desired rate in the GI tract, the ideal candidate polymer will also have at least a small amount of solubility in pH 6.8 media, permitting it to help stabilize dissolved active after release and prior to permeation through the enterocytes. We evaluated the ability of these polysaccharides to perform these roles with respect to curcumin, and compared them to the popular ASD polymer PVP.

3.1. Characterization of spray dried amorphous solid dispersions

Initially we evaluated the relative abilities of the three polymers to stabilize curcumin against crystallization in the solid phase, by preparing spray-dried dispersions of various concentrations of curcumin in these polymers and comparing with physical blends of the same composition. The blends were characterized by XRD, FT-IR, DSC and NMR spectroscopy.

XRD was used to investigate curcumin morphology in the polymer matrix. As can be seen from Fig. 2, the XRD patterns of all curcumin/CMCAB physical mixtures are similar to that of crystalline curcumin, with intensity proportional to percent curcumin; this indicated the continuing presence of crystalline curcumin and the ability to detect it down to as little as 10% by weight. In contrast, XRD patterns of all curcumin/CMCAB spray dried blends showed a halo pattern without diffraction peaks, indicating that curcumin is completely amorphous in CMCAB molecular blends even up to *90% curcumin*. Similarly, all curcumin/HPMCAS, CAAdP and PVP spray dried dispersions were amorphous (Supplementary Material Fig S2), but crystalline peaks were observed in all physical mixtures.

DSC is useful for investigating properties of small molecule/polymer blends, providing information not only about the drug physical state in the blend, but also polymer behavior. For polysaccharides containing both pendent carboxyl and hydroxyl groups (CMCAB, HPMCAS, CAAdP) transitions are observed above 200 °C that we ascribe to crosslinking esterification reactions. Therefore we carried out DSC analyses of mixtures containing these polymers at ≤200 °C. DSC heating curves of curcumin solid dispersions as well as those of pure curcumin and matrix polymers are shown in Fig. 3(A) and Fig S3. Fig. 3(B) shows T_g values of solid dispersions vs. Cur content. Cur used in these studies displayed a melting transition at 177 °C. Matrix polymers showed T_g values; CMCAB 141 °C, CAAdP 133 °C, HPMCAS 121 °C, PVP 175 °C. Cur/matrix physical mixtures had DSC glass transitions similar to those of pure polymers, and melting transitions similar to that of pure Cur. In contrast (Fig. 3(B)), T_g values of Cur ASDs were lower than those of the corresponding polymer, and decreased with increasing curcumin content, typical

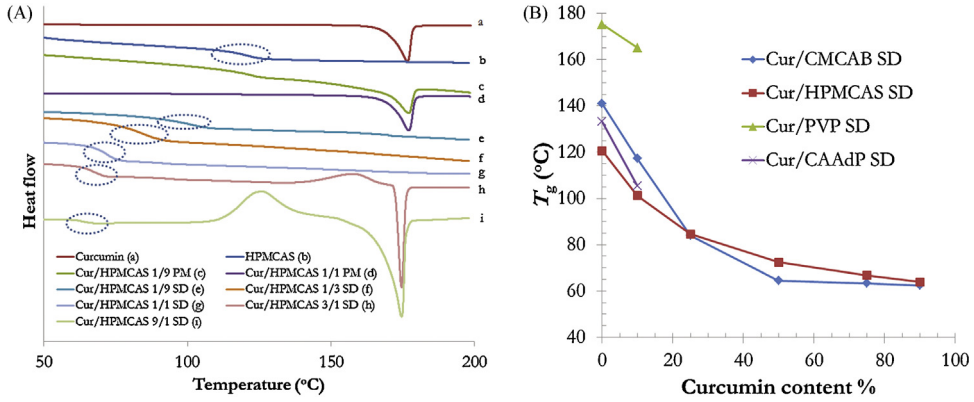

Fig. 3. (A) DSC heating curves of Cur, HPMCAS, Cur/HPMCAS physical mixtures and solid dispersions, glass transitions are indicated in dotted oval; (B) T_g values of Cur solid dispersions vs. Cur content.

for a small molecule plasticizer molecularly dispersed in a polymer matrix. At curcumin content ≤50%, no recrystallization and subsequent melting peaks were observed, indicating that Cur was amorphous and protected against crystallization even at high temperature. Interestingly, Cur melting endotherms were observed for CMCAB and HPMCAS ASDs with Cur content ≥75%, and in all four cases (Cur/CMCAB or Cur/HPMCAS, 3/1 and 9/1) exothermic Cur crystallization peaks were also observed. Melting transitions at Cur content >75% shifted from 176 to around 170 °C, which may indicate less perfect crystals than for pure Cur, or melting point depression resulting from intimate contact with the polymer. The contrast between XRD and DSC results indicates the potential for high temperature crystallization at ≥75% Cur, rather than the presence of detectable crystalline Cur in these blends at ambient temperatures. Similar DSC changes were observed in the Cur/PLGA (poly(lactic/glycolic) acid) system (Shahani & Panyam, 2011).

FTIR was used to explore curcumin–polymer matrix interactions. IR spectra of crystalline and amorphous Cur, HPMCAS and Cur/HPMCAS (1:3) solid dispersions are shown Fig. 4. The sharp band at ~3500 cm^{-1} and the broad peak centered at 3300 cm^{-1} in the crystalline Cur spectrum are attributed to OH stretching. In amorphous Cur, this peak broadens considerably with a maximum at around 3400 cm^{-1} and a shoulder at 3500 cm^{-1} suggesting a difference in the molecular environment of the hydroxyl groups in amorphous relative to crystalline Cur. The dispersion also shows broad peaks at 3500–3400 cm^{-1}, similar to bands seen in pure HPMCAS and pure amorphous Cur, confirming the dispersion's amorphous nature. However, the overall band shape cannot be recreated by simple addition of pure HPMCAS and amorphous Cur spectra, indicating curcumin–polymer interactions. Overall, the band shows greater intensity on the high wavenumber side in the presence of the polymer relative to pure amorphous Cur. Additional evidence of interactions can be seen from examining polymer carbonyl functions at 1743 cm^{-1}, where a shift to lower wavenumber (1737 cm^{-1} in 1:1 dispersion) is observed in the presence of Cur (Fig. 4(B)). For CAAdP and CMCAB similar changes were seen in the hydroxyl and polymer C=O spectral regions. For PVP-Cur dispersions, the Cur OH band frequency shifted to lower wavenumbers as did the polymer C=O band, indicating formation of stronger H-bonds in this system relative to the cellulosic polymers.

To confirm the absence of chemical reactions between Cur and the matrix, ^{1}H NMR spectra of spray dried ASDs were recorded (Fig S4). Spectra are simply additive of those of pure Cur and matrix polymer, with no new peaks or significant resonance shifts. These results support the conclusion that Cur is stable under the spray drying conditions, and unreactive with matrix polymers.

3.2. Contact angle of water on the solid dispersion film

We studied contact angles of water with Cur and Cur ASDs, as spin-coated films, following the hypothesis that wettability might influence dissolution rate. Contact angles of water on pure component films are: curcumin 102°, CMCAB 69.9° (Lit 69.5°), (Amim, Petri, Maia & Miranda, 2009) HPMCAS 58.9° and PVP 33.5°. As can be seen from Table 1, water contact angles of the ASDs are always higher than that of pure polymer but much lower than that of pure Cur; water contact angle increased with increasing [Cur]. Clearly wettability was influenced both by the concentration and nature of the polymer. Even the 90% solid dispersion displayed much lower water contact angle than that of pure Cur. Water contact angles of PVP and Cur/PVP 1/9 ASD decreased rapidly due to PVP water solubility, so it was difficult to study wettability using this method. However, the initial contact angles of PVP (33.5°) and Cur/PVP 1/9 SD blend (48.9°) were lower than the corresponding HPMCAS or CMCAB samples, as expected given PVP's water affinity.

3.3. Suppression of degradation

Cur degrades rapidly in aqueous solution, with accelerating rates as pH reaches 6.8 and above (Priyadarsini, 2009; Wang et al., 1997). Cur degradation products are shown in the Supplementary Material (Fig S5). HPLC of curcumin in ethanol (Fig S6) showed three peaks corresponding to curcumin, demethylcurcumin, and bis-demethylcurcumin. After incubation in aqueous buffer (pH 7.4 or 6.8, 24 h), several new peaks appear with retention times from 2 to 3.5 min, corresponding to curcumin degradation compounds including vanillin and ferulic acid, while peaks corresponding to curcumin are still strong. Only 36% of curcumin degraded after 24 h at pH 7.4 and room temperature (Fig S6(C)). Since the generation of supersaturated solutions of curcumin from amorphous solid dispersions can lead to both Cur degradation and recrystallization, we needed to employ a protocol that differentiates chemical

Table 1
Contact angles of water with films of curcumin, polymer matrices and Cur/polymer solid dispersions.

Substrate (Cur/polymer)	Cur/CMCAB	Cur/HPMCAS	Cur/PVP
100/0	102	102	102
90/10	77.3	66.4	–
75/25	77.7	65.7	–
50/50	77.7	65.2	–
25/75	76.2	61.4	–
10/90	74.3	60.4	48.9
0/100	68.9	58.9	33.5

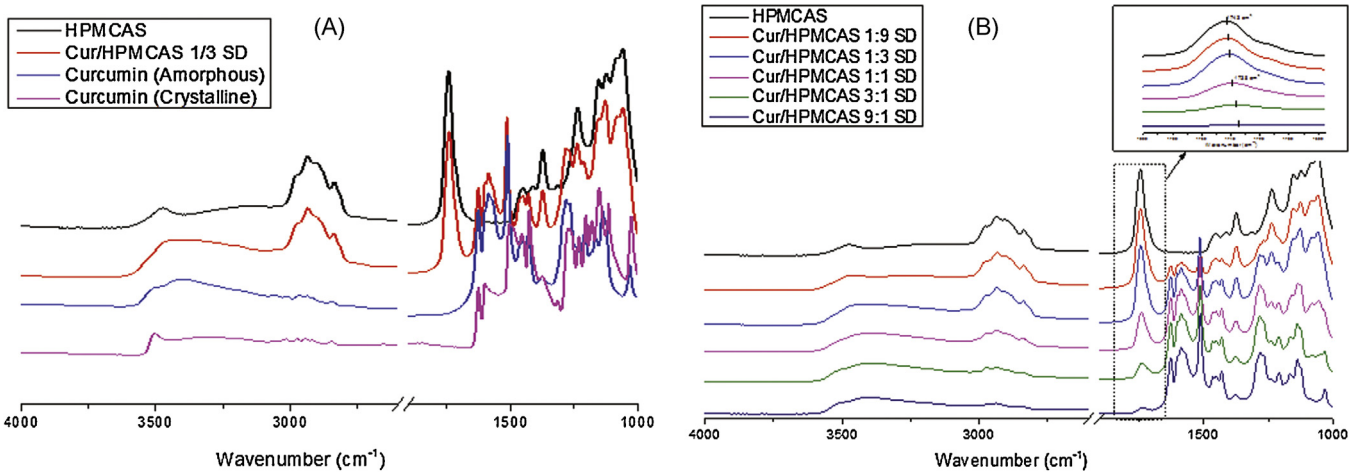

Fig. 4. (A) FTIR spectra of HPMCAS, 1:3 Cur/HPMCAS solid dispersion, curcumin (amorphous), and curcumin (crystalline). (B) FTIR spectra of HPMCAS and Cur/HPMCAS solid dispersions containing different amounts of polymer.

degradation from simple precipitation of Cur. We dilute the aqueous Cur solution with ethanol just prior to measurement, to ensure that any crystallized Cur is re-dissolved for detection. These results show that curcumin crystallizes in aqueous buffer, and that crystallized curcumin degrades more slowly; it is important in Cur stability studies to carefully separate effects of crystallization and degradation. In contrast to pure Cur, Cur/CMCAB 1/9 ASD shows enhanced Cur chemical stability in solution, with only 4% curcumin degradation detected after 24 h in pH 7.4 buffer (Fig S6(C)).

The impact of the polymers on curcumin degradation was further confirmed by UV–vis spectroscopy of Cur in pH 7.4 buffer; samples at each time point were diluted with an equivalent volume of ethanol just prior to measurement in order to dissolve any crystallized, but chemically intact Cur. After 24 h in pH 7.4 buffer (Fig. 5(A)), pure Cur has degraded by 33%, while only 11% of Cur in CMCAB ASD (1/9) has degraded. Similar stabilization is observed at pH 6.8 (Fig. 5(B)). These results confirmed that *CMCAB stabilizes curcumin and inhibits its degradation in aqueous buffer*. Analysis of Cur ASDs in the other polymer matrices under the same conditions indicated that ability to inhibit degradation follows this sequence: CAAdP > CMCAB > HPMCAS > PVP. This chemical stabilization, like stabilization against crystallization, is presumably due to solution interaction between the polymer and curcumin.

The contribution of crystallization to removal of Cur from solution is illustrated in Fig. 5(C and D), which shows UV–vis absorption of Cur and its ASDs in aqueous buffer (without ethanol dilution) versus time. Dissolved Cur (starting concentration 50 μg/mL) in both pH 7.4 (Fig. 5(C)) and 6.8 (Fig. 5(D)) buffers decreased after 5 h to 40% (pH 7.4) and 44% (pH 6.8) Cur remaining in solution. Since (Fig. 5(A and B)) Cur degrades far less than this after 5 h (7% at pH 6.8, 16% at pH 7.4), clearly crystallization dominates removal of Cur from solution under these conditions, further illustrating the importance of stabilization by polymers against crystallization. While 66% of pure Cur in pH 6.8 buffer solution had degraded or crystallized within 24 h, Cur in ASDs in PVP (19%) and HPMCAS (16%) degraded or crystallized to a much lesser extent over the same time period. The more hydrophobic *CMCAB and CAAdP stabilized curcumin against chemical degradation and crystallization in pH 6.8 buffer solution almost completely*, with 95–98% of curcumin remaining dissolved and intact after 24 h. This combined stabilization against degradation and precipitation is unprecedented to our knowledge; in fact, dissolution of molecularly dispersed Cur in HPMCAS has been observed to accelerate photochemical degradation vs. that of crystalline Cur, and stabilize it only slightly vs. dissolved Cur (Onoue et al., 2010a). Very recently, investigators have reported protection of the related flavonoid quercetin from degradation in alkaline solution by formulation as lecithin-based nanoparticles (Date et al., 2011). Polymer–drug association in solution may be necessary to prevent recrystallization; we know that these polymers can dissolve in pH 6.8 buffer at ≥ μg/mL levels (even though the bulk of CMCAB for example does not dissolve at that pH) (Alonzo et al., 2011). We hypothesize that such solution association is also the source of the chemical stabilization. Polysaccharide complexation with smaller organic molecules is well-known and quite selective in the case of the amylose helix or of cyclodextrin cavities, but such complexation is not well-known for cellulose derivatives. The observed stabilization addresses a major previous drawback to the therapeutic use of curcumin.

3.4. Dissolution testing and solution concentration enhancement

The extremely low Cur water solubility and the expected supersaturation achievable from ASDs create complex equilibria and analytical problems. For example, generating a Cur calibration curve including supersaturated concentrations is problematic; how to generate such concentrations in the absence of polymer? The generation of nanoparticles is also problematic; these may be formed by recrystallization from the supersaturated solutions. These are difficult to remove by filtration; even 20 nm syringe filters may not catch the smallest nanoparticles, and nonpolar solvates may adsorb onto filter media (Lindenberg, Wiegand & Dressman, 2005). Worse, nanoparticles can absorb UV light and therefore may be erroneously counted as dissolved active (Bohren & Huffman, 1983).

We chose to deal with these issues by generating calibration curves with solutions of curcumin in ethanol. We carried out necessary control experiments to show that the Cur extinction coefficient was not substantially changed by the addition of small amounts of water (up to 5 vol%; more could cause partial Cur crystallization). We attempted to remove any nanoparticles present by centrifuging before UV–vis measurements. This protocol gave highly repeatable values (error <5%). In the dissolution tests, after centrifugation Cur concentration was measured by UV–vis analysis of the supernatant (Fig. S7). It is apparent that lower Cur concentration in the solid ASD affords higher Cur percent release, when the polymer amount in the ASD samples is less than its maximum solubility, as is typical of ASDs (Simonelli, Mehta & Higuchi, 1976). Solution concentrations from HPMCAS dispersions are uniformly much higher than from equivalent CMCAB dispersions. One influence on the maximum Cur solubility attainable from these amorphous solid dispersions is the

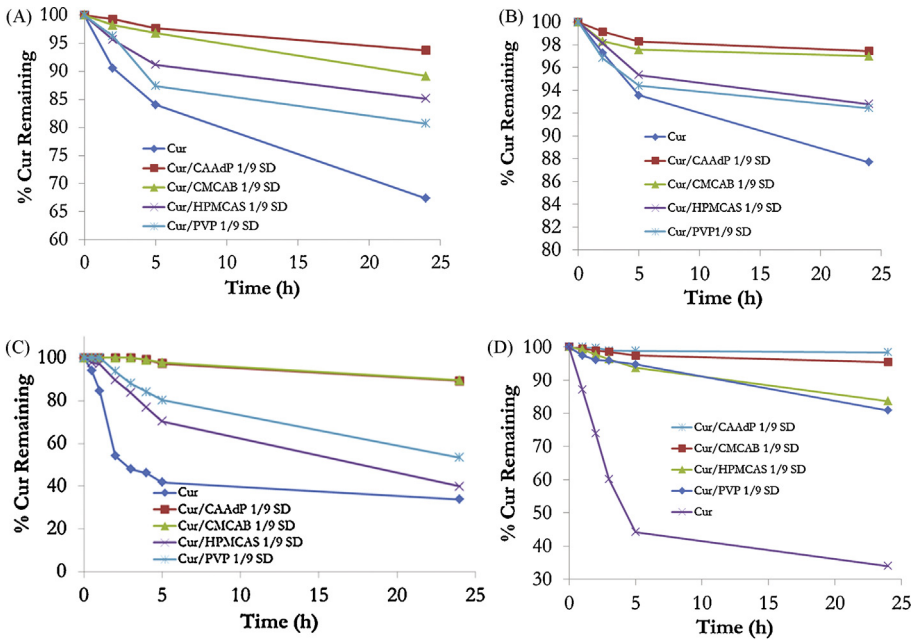

Fig. 5. Stability of Cur and Cur/polymer solid dispersions in pH 7.4 (A) and 6.8 (B) buffer (UV–vis after EtOH dilution); stability of curcumin and Cur/polymer solid dispersions in pH 7.4 (C) and 6.8 (D) buffer (UV–vis, no EtOH added).

Table 2
Solubility of polymers and maximum Cur concentration from their ASDs under different centrifugation conditions.

Polymer	Solubility in water (mg/mL)	Maximum Cur concentration (μg/mL) from amorphous dispersion vs. centrifugation speed (*g*)
PVP	>600	2900 (14,000 × *g*), 2600 (70,000 × *g*)
HPMCAS	23.4	260 (14,000 × *g*), 210 (70,000 × *g*)
CMCAB	1.6	1.8 (14,000 × *g*)
CAAdP	1.5	1.4 (14,000 × *g*)

relative aqueous solubility of the polymers (Table 2). Maximum [Cur] increases as polymer solubility increases. It is well recognized that polymers can increase solute equilibrium solubility (Tros de Llarduya, Martín, Goñi & Martínez-Ohárriz, 1998) and delay crystallization from supersaturated solutions.

Polymer solubility will influence active concentrations in at least two ways. Partial or total swelling or dissolution of the polymer matrix can serve as drug release mechanisms. The critical polymer stabilization of the active against crystallization from supersaturated solution also relies upon some degree of polymer dissolution.

The highest Cur release was only 50–60% even from the Cur/PVP 1/9 SD, which may be attributed to Cur degradation or precipitation in aqueous buffer. It is difficult to remove nanoparticles from dissolution test samples quantitatively by centrifugation; we routinely used centrifugation at 14,000 × *g* since it gave repeatable results, showing only slightly higher apparent solubility than at higher speeds (Fig S8), and avoided issues of inefficient filtration of very small particles or of absorption of solute onto the filter material.

3.5. Drug release profiles

In measuring drug release profiles in pH 6.8 buffer solution, maximum Cur concentration was fixed at 70 μg/mL. UV–vis absorption was measured and plotted vs. time (Fig. 6(A)). Fastest and most extensive Cur release was observed at the lowest Cur concentrations in the ASDs. Release was also faster and more complete with HPMCAS as compared with CMCAB. At 1:9 Cur/HPMCAS highest release (39%) was observed within 5 h and 43% after 24 h, vs. only 11% release from a 1:3 dispersion and 4.8% from 1:1 dispersion after 24 h.

To study the effect of polymer structure, drug release profiles at pH 6.8 from Cur/PVP 1/9, Cur/HPMCAS 1/9, Cur/CMCAB 1/9 and Cur/CAAdP 1/9 solid dispersions were compared (Fig. 6(B)) with pure curcumin and a physical mixture (Cur/HPMCAS 1/9). Release from the Cur/PVP 1/9 solid dispersion was fastest and

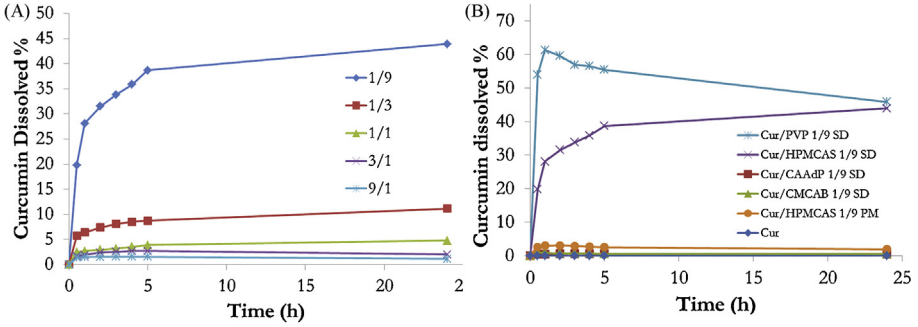

Fig. 6. (A) Dissolution from Cur/HPMCAS solid dispersions in pH 6.8 buffer with centrifugation at 14,000 × *g* for 10 min before UV–vis measurement; (B) dissolution of Cur and Cur physical mixture and spray-dried blends with polymers in pH 6.8 buffer with centrifugation at 14,000 × *g* for 10 min before UV–vis measurement.

most complete, reaching 61% within 1 h, while release from the Cur/HPMCAS 1/9 SD blend reached 44% within 4 h. Release from the hydrophobic CMCAB or CAAdP blends (1/9 SD) was quite slow and incomplete, reaching a maximum of only 0.6–0.7% after 3 h. Pure Cur release concentration was below the UV/Vis detection limit. Release from the Cur/HPMCAS 1/9 physical mixture was much slower and less complete than that from the ASD, reaching only 3.1% after 24 h. Clearly both PVP and HPMCAS are highly effective at suppressing Cur crystallization in both the solid and solution phases, leading to practical levels of Cur release within physiologically relevant time windows.

It is also of interest to compare Cur release from these solid dispersions under conditions similar to those of the stomach (pH 1.2 buffer, Fig. S9). Release from the PVP amorphous blend (Cur/PVP 1/9 SD blend) was substantial, reaching 54% Cur release within 2 h. In contrast, virtually no dissolution was observed from pure curcumin or its amorphous blends with CMCAB, CAAdP, or HPMCAS. Since PVP contains a slightly basic amide group, this result is exactly as expected. These results suggest that CMCAB, CAAdP and HPMCAS may protect Cur from the stomach contents much more effectively than would PVP.

4. Conclusions

Curcumin and the cellulose esters CMCAB, CAAdP and HPMCAS were readily blended by spray-drying, affording solid dispersions which were amorphous even at very high Cur levels. Release from CMCAB and CAAdP dispersions was quite slow and incomplete, probably due to the low wettability and low water solubility of these polysaccharide derivatives. In contrast, release from HPMCAS matrices was much faster; HPMCAS systems are comparable to PVP systems for solubilization and release of Cur, while showing better protection of Cur against stomach contents. Remarkably, HPMCAS, CAAdP, CMCAB and PVP amorphous dispersions all not only inhibited Cur crystallization in solution but also protected Cur against the chemical degradation to which it is quite prone, with CMCAB and CAAdP affording the best chemical stabilization. Systems based on the polysaccharide esters HPMCAS, CMCAB and CAAdP are promising for development of enhanced-bioavailability, curcumin-based therapeutic and dietary supplement formulations.

Supporting information available

Standard curves of curcumin UV–vis absorption vs. concentration in ethanol and in pH 6.8 buffer. XRPD patterns of Cur/HPMCAS, Cur/CAAdP and Cur/PVP spray dried solid dispersions. DSC heating curves of Cur, CMCAB, Cur/CMCAB physical mixtures and solid dispersions. ^{1}H NMR characterization of curcumin and curcumin/HPMCAS spray-dried dispersion. Figure describing curcumin chemical degradation. HPLC traces of curcumin and curcumin/CMCAB amorphous solid dispersions. Stability of Cur and Cur/CMCAB 1:9 solid dispersions in pH 7.4 buffer (HPLC after EtOH dilution). Maximum Cur concentration from Cur/CMCAB (A) and Cur/HPMCAS (B) solid dispersions at pH 6.8. Dissolution curves for curcumin/HPMCAS amorphous dispersions vs. centrifugation speeds. Dissolution of Cur and Cur in spray-dried blends with polymers in pH 1.2 buffer with centrifugation at 14,000 × g for 10 min.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.07.017.

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